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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,459	11/07/2001	David L. Lewis	Mirus.030.04	3774

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
12/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/007,459	LEWIS ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,14-16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 14-16, and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Remarks filed August 25, 2008.

Claims 11, 14, 15, 16, and 18 are pending in the instant application.

Claims 11, 14, 15, 16, and 18 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

37 C.F.R. § 1.131 Declaration

Applicant's Declaration filed under 37 C.F.R. § 1.131 and made of record August 25, 2008 is acknowledged and has been considered by the Examiner.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed March 21, 2008, claims 11, 14, 15, 16, and 18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24, 2005) in view of Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242, made of record in the previous Office Action mailed July 25, 2006), and Zhang et al. (Human Gene Therapy, 1999 Vol. 10:1735-1737, made of record in the previous Office Action mailed August 24, 2005). **This rejection is withdrawn** in view of Applicant's Declaration filed under 37 C.F.R. § 1.131. Specifically, the Declaration filed under 37 C.F.R. § 1.131 showed that Applicants conceived the teachings of Zhang et al. (Human Gene Therapy, 1999) prior to the effective date of the reference. That is,

Applicants conceived the theory of injecting DNA within 2 minutes as claimed in Applicant's claim 18 prior to the published teachings of Zhang et al. (Human Gene Therapy, 1999).

However, it should be noted that Applicant's Declaration filed under 37 C.F.R. § 1.131 is not sufficient enough to overcome the prior art reference of Zimmer (Methods, 1999). This is primarily due to the fact that the claims are drawn to a process for inhibiting expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising injecting a complex, wherein the complex comprises a double strand RNA oligonucleotide, where Applicant's Declaration filed under 37 C.F.R. § 1.131 reported results from a process for delivering nucleic acids in an *in vivo* parenchymal cell in a target tissue in a mammal. In fact, the end result of Applicant's Declaration focused on measuring gene expression and not gene inhibition. Furthermore, nowhere does Applicant's Declaration show that the nucleic acid delivered was a double strand RNA oligonucleotide. Because the end result of Applicant's Declaration concentrated on measuring luciferase gene expression, it appears that a double strand RNA oligonucleotide was never administered and gene inhibition was never a focus of the study.

Therefore, Applicant's Declaration filed under 37 C.F.R. § 1.131 is sufficient enough to overcome the prior art reference of Zhang et al. (Human Gene Therapy, 1999), but not sufficient enough to overcome the prior art reference of Zimmer (Methods, 1999).

After careful reconsideration of the claims, a new ground(s) of rejection is made of record as presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites, "The process of claim 13" in the preamble. Claim 18 recites, "The process of claim 17"in the preamble. There is insufficient antecedent basis for these limitations in the claims because claims 13 and 17 have been canceled. Accordingly, claims 14 and 18 have not been further examined on the merits because no meaningful search can be conducted on these claims since they are dependent on canceled claims, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24, 2005) in view of Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242, made of record in the previous Office Action mailed July 25, 2006).

Claim 11 is drawn to a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone; injecting a volume of a solution containing the complex into an efferent or afferent mammalian vessel of the target tissue *in vivo*, wherein the rate of injection and the volume of the solution increase permeability of a vessel within the

target tissue thereby delivering the double strand RNA oligonucleotide from inside the vessel, through a wall of the vessel, into the extravascular space and into the *in vivo* parenchymal cell, wherein the double strand oligonucleotide inhibits expression of the gene. Claims 15 and 16 depend from claim 11 and include all the limitations of claim 11 with the further limitations wherein the complex has a positive charge or a negative charge.

It is noted that the instant specification does not define the term, "target tissue". Therefore, the Examiner is interpreting this term broadly to include any tissue, but more specifically the site of injection. It is also noted that the instant specification at page 5, last paragraph discloses, "Permeability is defined here as the propensity for macromolecules such as polynucleotides to move through vessel walls and enter the extravascular space".

Determining the scope and contents of the prior art

Zimmer teach delivering an antisense oligonucleotide complexed with positive and negative charged polymers into a liver cell via tail vein injection (see Abstract and discussion at page 292). Specifically, Zimmer teach mixing an antisense and a polymer, wherein the zeta potential of the complex is less negative than the zeta potential of the antisense alone (see Table 2 and page 290, first full paragraph, which states, "at a lower ratio the surface charge of the nanoparticles is decreased by the ODNs as indicated by a decreased ζ potential"). Zimmer teach Protocol A, which provides cationically (positively) charged oligonucleotide-loaded nanoparticles and Protocol B, which provides anionically (negatively) oligonucleotide-loaded nanoparticles

(see page 287, first and second paragraphs). It is noted that Zimmer teach that the antisense nanoparticle complexes were injected into the tail vein at 5 nmol/5 ml/kg. It is noted that, given the definition of "Permeability" in the instant specification as discussed above, the Examiner is interpreting that the 5 nmlo/5 ml/kg injection volume increased permeability within the target tissue since the ribozyme complex moved through the vessel walls of the jugular vein and entered the extravasuclar space, ultimately reaching the liver. It is also noted that that the Examiner is of the opinion that the pressure against the vessel walls would inherently be increased because the needle used to deliver the oligonucleotide complexed with positive and negative charged polymers is external to the tail vein. The Examiner is also interpreting the tail vein to be the vessel, where the oligonucleotide obviously traveled from inside the vessel into the extravascular space to finally reach the liver cell.

It is noted that Zimmer are silent regarding whether or not the antisense oligonucleotide complexed with positive and negative charged polymers delivered into liver cells via tail vein injection inhibited expression of a target gene. However, the burden of establishing whether the prior art antisense oligonucleotide complexed with positive and negative charged polymers has the function of inhibiting gene expression, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound

basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Also, see *In re King*, 801 F.2d 1324, 1327, 231 USPQ 136, 139 (Fed. Cir. 1986). Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide complexed with positive and negative charged polymers taught by Zimmer would or would not have the additional functional limitation of inhibiting expression of a gene, as instantly claimed.

Ascertaining the differences between the prior art and the claims at issue

Zimmer do not teach a double stranded RNA oligonucleotide.

Vaish et al. teach that single stranded antisense oligonucleotides and double stranded ribozymes are two approaches that use similar techniques to achieve the same goal (see page 5239, first column). For example Vaish et al. teach, "The first step for inhibition of gene expression by a ribozyme is its binding to the mRNA. This step is akin to the antisense oligodeoxynucleotide method (AS-ODN) used for the same purpose. It is, therefore, not surprising that both approaches benefit from experience in each others areas".

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to devise a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone using the teachings of Zimmer and following the teachings and motivation of Vaish et al.

One of ordinary skill in the art would have been motivated to devise a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone since Zimmer taught that such a process could be used for nucleic acid gene therapy. One of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide taught by Zimmer with a double stranded RNA oligonucleotide as instantly claimed since Vaish et al. taught that antisense oligonucleotides and double stranded ribozymes function in a manner similar and it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

One would have had a reasonable expectation of success at devising a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone because Zimmer clearly teach the successful use and delivery of an antisense nucleic acid to a liver cell *in vivo* and since antisense and dsRNA are both sequence specific nucleic acid inhibitors of gene expression and are art-recognized functional and structural equivalents, the substitution of one known element for another would have yielded predictable results at the time of the invention.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-

8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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December 20, 2008
/Terra Cotta Gibbs/